IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
TRENTON DIVISION

CHRISTINE JANKOWSKI, et al, Plaintiffs, v. ZYDUS PHARMACEUTICALS USA, INC. and DOES 1-50, Inclusive., Defendants.	DOCKET NO.: 3:20-cv-2458-MAS-TJB Judge: Michael A. Shipp Magistrate Judge: Tonianne J. Bongiovanni

ZYDUS PHARMACEUTICALS USA, INC.'S REPLY BRIEF IN FURTHER SUPPORT OF ITS MOTION TO DISMISS PLAINTIFFS' SECOND AMENDED COMPLAINT

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Zydus Pharmaceuticals USA, Inc. ("Zydus") submits this Reply Brief in further support of its Motion to Dismiss Plaintiffs' Second Amended Complaint ("SAC") against Zydus.

Plaintiffs have now abandoned the causes of action for failure to warn based on a failure to distribute the medication guides and fraud. Having accepted that the label and warnings approved by the FDA were adequate, plaintiffs seek to provide life support for their complaint arguing that Zydus is liable for failing to provide 220 or more prescribing physicians with warnings about amiodarone.

Plaintiffs' prior opposition to Defendant's Motion to Dismiss plaintiff's first amended complaint ("FAC") (Dkt 17), argued that Zydus failed to warn in failing to provide consumer warnings – medication guides – to the plaintiffs, pharmacies, and physicians. *See* Pltf Opp, Dkt 17, at 1-3. Plaintiffs only reference their physicians was associated with an allegation that Zydus failed to provide, and properly distribute, medication guides, and that Zydus failed to report all adverse events to the FDA. *Id*.

In support of this newly crafted argument, plaintiffs contend that Zydus had no amiodarone label/warning in the third-party resource known as the Physician Desk Reference ("PDR") and further that Zydus failed to communicate the entirety of the amiodarone label/warnings to physicians.

I. Plaintiffs Fail to Overcome the Rebuttable Presumption that the Warning was Adequate

It is well-settled in New Jersey that a "pharmaceutical warning is presumed to be adequate as a matter of law if it is FDA-approved." *Nelson v. Biogen Idec, Inc.*, No. CV127317JMVMF, 2018 WL 1960441, at *9 (D.N.J. Apr. 26, 2018). Under the New Jersey Product Liability Act, which subsumes all actions for product liability, if a drug warning is FDA-approved, it creates a rebuttable presumption that the warning or instruction is adequate. N.J. STAT. ANN. 2A:58C–4.

Plaintiffs do not dispute that the content of Zydus' amiodarone warning label was adequate. *See* Pltf. Opp., at 2 ("Plaintiffs do not allege that Defendant should have changed the FDA warning at all."). To overcome the rebuttable presumption, a plaintiff asserting a failure to warn claim based on an inadequate warning must plead **specific** factual allegations of "deliberate concealment or nondisclosure of after-acquired knowledge of harmful effects," or "manipulation of the post-market regulatory process." *See Rowe v Hoffman-La Roche, Inc*., 189 N.J. 615, 626 (2007); *Perez v. Wyeth Labs., Inc.,* 161 N.J. 1, 24 (1999); *McDarby v. Merck & Co.,* 401 N.J. Super. 10, 62 (App. Div. 2008). Plaintiffs have not pled any specific allegations about Zydus' conduct other than speculative and generalized allegations that the warnings were not published in the PDR and Zydus "misled" physicians into believing amiodarone could be prescribed for atrial fibrillation.

Plaintiffs cannot overcome the rebuttable presumption established under New Jersey law, and as a result, Zydus' warnings must be deemed adequate as a matter of law.

II. As a Matter of Law, Adequacy of the Warning Does Not Require Proof that the Manufacturer Directly Provided Label Warnings to Physicians

There is no dispute that this jurisdiction has adopted the learned intermediary doctrine with respect to the manufacturer's duty to warn. *Niemiera v. Schneider*, 114 N.J. 550, 559 (1989). In *Niemiera*, the New Jersey Supreme Court recognized that a pharmaceutical manufacturer discharges its duty to warn the user of prescription drugs by making available prescription information, i.e., the label, to the prescribers who are in the best position to exercise medical judgment and inform the patient. *Id.* at 559-561.

The prescribing physician is under an obligation to disclose to a patient all material information that a "prudent patient" might find significant for a determination whether to undergo the proposed therapy. *Largey v. Rothman*, 110 N.J. 204, 211-212 (1988). It is the doctor who needs to educate himself or herself on the drug and convey this knowledge to the patient prior to prescribing the drug, pursuant to the medical standard of care.

For this reason, a manufacturer that provides a proper and adequate warning "may reasonably assume that the physician will exercise his informed judgment in

the patient's best interests." *See, In re Accutane Litigation,* No. 271, 2016 WL 5958375 at *5 (N.J. Super. Law Div. Oct. 12, 2016).

There is no dispute in this action that Zydus had an FDA approved warning. Nor is there any dispute that the brand or the other many generic versions of amiodarone had adequate warning.

The legal viability of the SAC is now founded on plaintiffs' argument that Zydus did not fulfill its duty to "provide" an adequate warning absent directly *communicating* the label warnings to the plaintiffs' prescribing physicians and that these physicians had inadequate information regarding the drug, i.e., that it had not been approved by the FDA for treatment of atrial fibrillation.

However, in constructing this legal fiction, the SAC and opposition to this motion assert contradictory allegations. On one hand, plaintiffs contend that Zydus never placed warnings for amiodarone in a reference resource for physicians (the "PDR") for amiodarone from 2008 to 2016 and that the prescribing physicians received no warnings, but then alleged "the prescribing physicians read and relied on the PDR, Epocrates app or other prescribing reference sources in prescribing Amiodarone to Plaintiffs". *See* Pltf Opp., at 6; *see also* Pltfs SAC ¶ 201.

The plaintiffs' construction of the word "provide" is impractical and unreasonable and without any legal foundation in either decisional or statutory law. As a matter of law, the defendant's obligation as a drug manufacturer is fulfilled by

having an FDA-approved label. It is the learned intermediary – the medical community – in fulfilling its standard of care, that must exercise its judgment and avail itself of the information in the public domain to educate itself regarding a drug prior to providing a patient with a prescription.

Once a drug is FDA-approved, the FDA requires that the prescribing information is distributed with the drug product or package from which a prescription drug is to be dispensed. *See* 21 CFR 201.100(c)(1). Plaintiffs have not alleged that the package inserts did not include the appropriate warnings nor that they were not distributed with the drug product.

Plaintiffs contend that even though Zydus provided its warning through package inserts with the medication, it was insufficient because package inserts were shipped with the medication and physicians would not typically receive the actual medication. The fact of the matter is, Zydus complied with the law. Zydus distributed its FDA-approved warnings, with its drug product pursuant to the law. Compliance with FDA regulations in having an FDA-approved label provides "compelling evidence that the manufacturer satisfied its duty to warn the physician." *Perez v. Wyeth Lab. Inc*., 161 N.J. 1, 24, 734 A.2d 1245 (1999).

The New Jersey Supreme Court held that "[t]he decision to prescribe a particular drug ultimately is a matter of judgment for the physician. In addition to considering the individual patient, the physician may consider all available

information concerning a drug. The information may include the manufacturer's inserts and PDR warnings, as well as medical journals, advice from colleagues, and the physician's own experience." *Morlino v. Medical Center of Ocean County*, 152 N.J. 563, 581 (1998). The Court further held that package inserts and the PDR alone do not establish the standard of care for physicians. *Id*. at 580. "[A] physician's failure to adhere to PDR warnings does not by itself constitute negligence." *Id*. "To confine the treatment choices to those expressly permitted in the PDR would be too restrictive. Such an approach also would be inconsistent with the FDA's position that physicians are not bound by PDR recommendations." *Id.* at 581.

"After a drug has been on the market for a sufficient period of time, moreover, physicians may rely more on their own experience and the professional publications of others than on a drug manufacturer's advertisements, inserts, or PDR entries." Id. at 580.

There is no allegation that any physician prescribed "Zydus amiodarone." Whether the plaintiffs or their family members received a Zydus form of amiodarone would only have been a consequence of what the dispensing pharmacy had in their inventory. It is unreasonable to impose a duty on Zydus to warn prescribing physicians writing generic prescriptions for amiodarone (divorced from any reference to a Zydus product) based on the patients post prescription receipt from their dispenser of a Zydus version of the product.

Plaintiffs' effort to assert that Zydus had a legal duty to provide the prescribers with an amiodarone warning also relies on a false premise – that the physicians had no legal duty to inform themselves about the drug and had no recourse to the necessary information regarding amiodarone. The assumption is that without receiving a label in hand, the physicians could not avail themselves of a warning.

In opposition plaintiffs rely on one outlier decision from a Minnesota state trial court, applying Minnesota law, which has no precedential effect on this Court. *Walsh v. Upsher-Smith Labs., Inc*., 2021 Minn. Dist. LEXIS 430, *19 (Oct. 4, 2021). The Court in *Walsh* relied on and misinterpreted an 8th Circuit decision. In *Schedin v. Ortho-McNeil-Janssen Pharms, Inc.*, 700 F.3d 1161, 1167 (8th Cir. 2012), the 8th Circuit held that a jury could determine whether a pharmaceutical company's *method* of communicating FDA warnings was sufficient. However, as the Circuit Court had noted, Minnesota law differed from many jurisdictions because the law had not addressed whether a package insert insulated a drug manufacturer from a failure to warn claim. In stark contrast, New Jersey law employs a rebuttable presumption that the drug warning labels are adequate if they are FDA-approved. Additionally, *Schedin* dealt with a brand manufacturer that had changed its warnings. Liability focused on whether *new* warnings were communicated to the doctors. *Id*. In the case at bar the warnings at issue are not new warnings but the same warnings that were FDA-approved for the brand manufacturer's label in 1985.

Plaintiffs have not alleged that their prescribing physicians only relied upon Zydus for a warning – out of over a dozen other amiodarone manufacturers, plus the brand, Cordarone®. As stated in defendant's memorandum of law, there are over a dozen generic manufacturers of amiodarone and a brand manufacturer of Cordarone® that have the exact same label/prescribing information. *See* Defendant's Memorandum of Law, Dkt 36, at **Exhibit H.** The SAC is fatally deficient because plaintiffs do not allege that all Amiodarone or Cordarone® labels were unavailable in the public domain.

Plaintiffs, therefore, ask this Court to accept a fiction that these physicians were unaware of the label warnings from public domain sources typically relied upon by the medical community to satisfy its standard of care in prescribing medications.

No database, desk reference, web site (including the FDA websites) relied on Zydus to publicly provide the warning. Physicians do not need to only obtain a package insert from a Zydus amiodarone vial since they are not prescribing Zydus amiodarone – they are simply prescribing generic amiodarone which could be supplied by a dozen different manufacturers.

There is an absurdity to plaintiffs' contentions when considered in the context of a drug with over a dozen manufacturers publishing the exact same warnings. The warnings associated with Amiodarone/Cordarone®, have been FDA-approved and

available for physician review for over thirty years. Zydus was not the lone manufacturer of a new drug. Zydus' approval to market amiodarone was in 2008. The brand was approved in 1985 and by the time of the earliest of the plaintiffs' prescriptions, amiodarone had been on the market as distributed by either the brand manufacturer or other generic manufacturers.

In opposition plaintiffs rely on their representation that the PDR failed to include a "Zydus" amiodarone label or warning. As noted above, the amiodarone warning is not unique to Zydus, it is a generic warning the plaintiffs glaringly omit never addressing that there is a generic warning available to the prescribing community for physicians to fulfill their standard of care.

Plaintiffs do not cite state or federal law that would require a pharmaceutical drug's prescribing information be published in the PDR, or that the failure to do so is actionable. The PDR is an available third-party resource for physicians to access prescribing information. The PDR site does not identify Amiodarone by each individual manufacturer. Rather, it publishes one drug summary and label for each drug that has been approved by the FDA.[1] The publication in the PDR is not specific to Zydus, nor is it controlled by any statutory rule. As a result, this fact does not

[1] See PDR website at https://www.pdr.net/drug-summary/Amiodarone-Hydrochloride-Injection-amiodarone-hydrochloride-3234.8358 (last visited October 27, 2021). The Court may take judicial notice of public records and government websites in deciding a Motion to Dismiss. *See* Fed. R. Evid. 201.

control whether Zydus' warnings were adequate and communicated appropriately, as a matter of law.

There are over 20,000 prescription drug products approved by the FDA in the United States.[2] Plaintiffs presume that every doctor in the country should be personally receiving over 20,000 different drug labels, whether or not they prescribe the medication in their own practice.

It should be noted that the New Jersey Model Civil Jury Charges for a failure to warn claim indicates that a product is defective if the product "fails to contain an adequate warning or instructions." Model Jury Charge (Civil) 5.40C. There is no requirement in the Model Jury Charges to *directly* warn patients and physicians. Even where the Model Jury Charges explains that "[i]n the case of prescription drugs, the warning must be one that a reasonable prudent manufacturer would have provided to adequately communicate information on the dangers and safe use of the product to physicians," the charge is not adding a requirement to directly warn physicians and patients, but defining an adequate warning under the law (i.e. one that communicates sufficient information to physicians). *Id*.

Moreover, plaintiffs wrongly imply that off-label for atrial fibrillation is per se tortious. This ignores the surplus of medical research, clinical trials, reports,

[2] See U.S. Food & Drug Administration Fact Sheet: FDA at a Glance, updated November 2021. https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance

journals and the medical standard of care surrounding the use of amiodarone for atrial fibrillation. "Off label" use for the treatment of atrial fibrillation was within the Clinical Practice Guidelines for the "Management of Patients with Atrial Fibrillation," published by the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society before Zydus received FDA approval in 2008.[3] These guidelines are based on medical professionals analyzing clinical data, conducting clinical trials and studies, cases studies, consensus opinion of experts, and the standard of care.

It is unreasonable and impractical (and without any legal support) to ask this Court to create an actionable claim against a generic product manufacturer for failing to expressly notify each physician in the United States of label information. It invites in this case over a dozen mailings by manufacturers of the same drug. It ignores the fact that there is no direct relationship between the physician and the generic manufacturer, nor is one alleged. Most importantly, it is unsupported by any legal precedent.

[3] See 2006 and 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation at https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.177292; 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation | Circulation (ahajournals.org).

III. Zydus' Amiodarone Warnings Are Deemed Published When the FDA Approves it Drug.

Under the U.S. Code of Federal Regulations, once a generic drug is approved, the Secretary of Health and Human Services shall, every thirty days, "revise the list to include each drug which has been approved for safety and effectiveness". *See* 21 U.S.C. 355 (j)(7)(A)(ii). The regulation further states that a drug approved for safety and effectiveness, shall be considered "published" on the date of its approval. *See* 21 U.S.C. 355 (j)(7)(B). "The Secretary shall post on the Internet Web site … the approved professional labeling and any required patient labeling of a drug approved under this section or licensed under such section 262 not later than 21 days after the date the drug is approved or licensed, including in a supplemental application with respect to a labeling change." *See* 21 U.S.C. 355 (r)(3).

The federal regulations specifically provided that as of September 2007, before Zydus' amiodarone was approved, the FDA would supply all drug information electronically on its web site to improve communication of drug safety information. [4]

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[4] (r) **Postmarket drug safety information for patients and providers**

(1) Establishment

Not later than 1 year after September 27, 2007, the Secretary shall improve the transparency of information about drugs and allow patients and health care providers better access to information about drugs by developing and maintaining an Internet Web site that--

(A) provides links to drug safety information listed in paragraph (2) for prescription drugs that are approved under this section or licensed under section 262 of Title 42; and

(B) improves communication of drug safety information to patients and providers.

(2) Internet Web site

The Secretary shall carry out paragraph (1) by--

The information published on these web sites includes patient labeling, patient package inserts, medication guides, recent safety information and alerts about the drug, product recalls, warning letters, guidance documents, among other pertinent documents. *See* 21 U.S.C. 355 (r)(2)(B). Not only is the label information distributed in hard copy with the medication itself, pursuant to 21 CFR 201.100(c)(1), but the FDA has a procedure for making every FDA-approved drug's labeling available electronically. Zydus' label has been published on federally run websites like DailyMed for over a decade. *See* MOL, fn 12.

Additionally, FDA Guidance documents explain this process. Upon FDA-approval of a prescription drug, the approved written warnings are published by the FDA in the "Approved Drug Products With Therapeutic Equivalence Evaluations" also referred to as the "Orange Book."[5] The Orange Book is updated on a monthly basis (electronic version is updated on a daily basis) to include newly approved drugs, or remove drugs that have been withdrawn from the market. *Id*. When prescription drugs are approved by the FDA, they are made available on an FDA

> **(A)** developing and maintaining an accessible, consolidated Internet Web site with easily searchable drug safety information, including the information found on United States Government Internet Web sites, such as the United States National Library of Medicine's Daily Med and Medline Plus Web sites, in addition to other such Web sites maintained by the Secretary…

[5] Orange Book, Questions and Answers, Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, May 2020, https://www.fda.gov/media/138389/download

website called Drugs@FDA.[6] "In addition, FDA facilitates the availability of up-to-date drug prescribing information in an easily accessible electronic format on the National Library of Medicine Web site at DailyMed." *Id*. at 7.

A manufacturer's duty to provide warnings and instructions for use to prescribers is satisfied with FDA approval of a label and incorporation of the label in the package insert. The prescribing information is further communicated by its publication on various governmental websites (such as the Orange Book, PDR, DailyMed and Drugs@FDA).

IV. Plaintiffs Failed to Plead Claims to Survive FRCP 8(a)(2)

An allegation of off label promotion is not an actionable tort unless it is a misstatement, a misrepresentation, or a fraud. Plaintiffs have abandoned allegations or causes of action of fraud. While plaintiffs cite instances of brand manufacturer and third-party application purported misrepresentations, there is no allegation of any specific misrepresentations about Amiodarone by Zydus.

Plaintiff provides no specific factual allegations that would rise to the level of a claim under the federal rules. A pleading must have factual and evidentiary support (FRCP 11(b)(3)) and if such factual contentions are lacking, federal rules require dismissal. FRCP 8(a). Dismissal is warranted if a complaint merely contains "naked

[6] Drug Safety Information – FDA's Communication to the Public, U.S. Department of Health and Human Services, Food and Drug Administration, March 2012, https://www.fda.gov/files/drugs/published/Drug-Safety-Information----FDA%27s-Communication-to-the-Public.pdf; see also, https://www.accessdata.fda.gov/scripts/cder/daf/

assertions devoid of further factual enhancement," *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009).

Over two hundred plaintiffs are unable to identify one instance of Zydus misrepresenting the uses and risks of amiodarone, citations or sanctions by the FDA over the last eleven years for failing to publish its label/warnings, or one physician that confirms they cannot, and have never been able to, access Zydus' amiodarone warnings. Plaintiffs do not allege a *single instance* in which Zydus engaged in any misleading or deceiving behavior, nor do they plead any facts to support a conspiracy to promote off-label use of amiodarone.

V. CONCLUSION

For the foregoing reasons, Zydus respectfully requests that this Court dismiss Plaintiffs' Second Amended Complaint under Fed R. Civ. P. 12(b)(6) and 8(a). Because any potential amendment would be futile and subject to dismissal for the same reasons, Zydus requests dismissal with prejudice and without leave to amend.

Dated: December 17, 2021

Respectfully submitted,

MORRISON MAHONEY LLP

By: */s/ Kateryna Stupnevich*
Kateryna Stupnevich, Esq.
kstupnevich@morrisonmahoney.com
Arthur J. Liederman *(to be admitted pro hac)*
aliederman@morrisonmahoney.com
Nicole M. Battisti *(to be admitted pro hac)*
nbattisti@morrisonmahoney.com
Wall Street Plaza
88 Pine Street, Suite 1900
New York, NY 10005
Phone: 212-825-1212
Fax: 212-576-8934

Attorneys for Defendant
ZYDUS PHARMACEUTICALS USA, INC.

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that a true and correct copy of the foregoing **ZYDUS PHARMACEUTICALS USA, INC.'S REPLY BRIEF IN FURTHER SUPPORT OF ITS MOTION TO DISMISS PLAINTIFFS' SECOND AMENDED COMPLAINT** has been served this 17th day of December, 2021, on the following counsel, via the Court's ECF by electronic mail on the following:

ANTHONY SCOTT PINNIE
PINNIE LAW OFFICE
334 WEST FRONT STREET
MEDIA, PA 19063
610-892-9200
EMAIL: APINNIE@PINNIELAW.COM

/s/ Kateryna Stupnevich
KATERYNA STUPNEVICH